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Study protocol for the evaluation of Managing Cancer and Living Meaningfully (CALM) in people with advanced non-small cell lung cancer treated with novel therapies

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Study protocol for the evaluation of Managing Cancer and Living Meaningfully (CALM) in people with advanced non-small cell lung cancer treated with novel therapies

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Abstract

Objectives. People with advanced non-small cell lung cancer (NSCLC) treated with immunotherapies or targeted therapies may have improved outcomes in a subset of people who respond, which has raised unique psychological concerns requiring specific attention. These include the need for people with prolonged survival to reframe their life plans, and to tolerate uncertainty related to treatment duration and prognosis, creating the requirement for tailored health information. A brief intervention for people with advanced cancer called Managing Cancer and Living Meaningfully (CALM) could be suitable to help people treated with novel therapies address these concerns. However, CALM has not been specifically evaluated in this population. This study aims to evaluate the acceptability and feasibility of CALM in people with advanced NSCLC treated with novel therapies and obtain preliminary evidence regarding its effectiveness in this population.

Methods and analysis. Twenty people with advanced or metastatic NSCLC treated with targeted- or immuno-therapy will be recruited from a single comprehensive cancer centre in Melbourne, Australia. Participants will complete 3-6 sessions of CALM delivered over 3-6 months. Participants will complete outcome measures at baseline, post-intervention, 3-months, and 6-months. Measures include the Patient Health Questionnaire (PHQ-9), Death and Dying Distress Scale (DADDS), Functional Assessment of Cancer Therapy General (FACT-G) and Clinician Evaluation Questionnaire (CEQ). The acceptability of CALM will be assessed using patient experiences surveys, qualitative interviews with participants with cancer and their carers, and three CALM therapists. Feasibility will be assessed by analysis of recruitment rates, treatment adherence, and intervention delivery time.

Ethics and dissemination. Ethics approval has been granted by the [hospital] Human Research Ethics Committee. Results will be made available to funders, and broader clinicians and researchers through conference presentations and publications in peer-reviewed journals. If CALM is found to be acceptable in this cohort, this will inform a potential Phase 3 trial.

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Strengths and Limitations

- This is one of the first studies to examine the acceptability of a psychological intervention specific for advanced disease in people with advanced NSCLC treated with immunotherapies or targeted therapies.
- The use of mixed methods will capture detailed qualitative and quantitative information on the acceptability of CALM in this cohort.
- The findings will inform the clinical application of CALM in this cohort, as well as informing future research to evaluate its efficacy in this population.
- The primary limitation of this study is the small sample size limiting interpretations on efficacy.

Keywords

Non-small cell lung cancer, psychological therapies, CALM, supportive care, immunotherapy, targeted therapy

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Background

Advanced non-small cell lung cancer (NSCLC) has historically had a poor prognosis, with five-year overall survival approximately 6% [1]. In recent years, however, improved understanding of molecular subtypes of metastatic NSCLC and the introduction of immunotherapies (IT) and targeted therapies (TT), (subsequently referred to as 'novel therapies'), has improved the prognosis for a subset of people with metastatic NSCLC. For example, five-year overall survival rate is now 62.5% for people with advanced NSCLC with anaplastic lymphoma kinase (*ALK*) translocations who received first-line alectinib [2], and 31.9% for people with cancers that have a programmed death ligand-1 (PDL-1) with tumour proportion score ≥50% who received first-line pembrolizumab [3]. This growing number of people living with advanced NSCLC who experience durable tumour responses to modern treatment approaches may have unique psychological needs [4,5,6,7].

A recent qualitative study of people with NSCLC treated with immunotherapy or targeted therapy found significant unmet needs, including: difficulty managing treatment side effects and toxicities; uncertainty regarding prognosis and treatment duration; not fitting into the 'sick' role; and the emotional strain of seeking tailored health information [4]. Similar concerns have been identified in this cohort in the United States [5, 6], the United Kingdom and Denmark [5]. These concerns can have a significant impact on quality of life, decision-making, and health information-seeking behaviours [5]. There is therefore an urgent need to address the unique psychological concerns of people with advanced NSCLC treated with these novel therapies.

The few psychological interventions trialled in people with metastatic cancer treated with novel therapies have limited their focus to a single area, such as fear of cancer recurrence [8], or promoting hope [9], or have been limited to a single psychological consultation delivered to only two participants [10]. Whilst these have shown promise in addressing these specific areas, they are unlikely to address the broader range of needs identified in the qualitative studies specific to people with advanced NSCLC who have been treated with novel therapies. Managing Cancer and Living Meaningfully (CALM) is a brief evidence-based intervention for people with advanced cancer that has potential to address broader psychological concerns in this population related to four content domains [11]. These are: 1) symptom management and communication with healthcare providers; 2) changes in identity and relationships; 3) sense of meaning and purpose; 4) sustaining hope and facing mortality. CALM is intended to help people attend to the dual tasks of preparing for progressive disease and end-of-life, whilst simultaneously focusing on living (a challenge identified by this cohort [5]). CALM has been shown to reduce depressive symptoms, improve preparation for end-of-life [12] and is associated with subjective improvements in relationships, communication, values identification, and reduced concerns about the future [13].

Though CALM is currently being trialled in other cohorts, such as people with primary malignant brain tumours [14], it has not yet been specifically studied in people with advanced cancer treated with novel therapies. Unlike the cohort in the original CALM randomised controlled trial (RCT) [12] who had a 12-18 month prognosis, people with advanced NSCLC treated with novel therapies may live longer with their disease. It is essential to examine the feasibility and acceptability of CALM in this unique population before undertaking larger-scale studies to evaluate its efficacy.

The overall aim of the present study is to assess the acceptability, feasibility and preliminary evidence of potential impact of CALM in people with advanced NSCLC treated with novel therapies. The specific objectives of this project are to:

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1. Assess the feasibility of the CALM intervention, outcome measures, and study design to guide the development of a possible subsequent Phase 3 RCT;
2. Explore the acceptability of CALM for people with advanced NSCLC treated with novel therapies, their carers, as well as for therapists delivering the CALM intervention;
3. Provide preliminary evaluation of the potential impact of CALM in this population.

Methods and Analysis

Study design

This study is a prospective single-arm pilot study. A mixed methods design will be used. The study adheres to the SPIRIT checklist (see Additional File 1).

Patient involvement

This pilot study was conceived and designed by a multidisciplinary group of clinicians, researchers, and people with a lived experience of lung cancer ('patient representatives'). Patient representative co-investigators were intimately involved in the design of this project, and will continue to be involved in management oversight through membership of the steering committee. Feedback from participants with cancer and their carers will be provided through a patient experiences survey and qualitative interviews regarding their experience of the intervention and their satisfaction and level of burden with the intervention. This will inform the intervention delivery in a future randomised controlled trial.

Participants

Twenty people with advanced or metastatic NSCLC treated with novel therapies will be recruited from outpatient clinics at an Australian comprehensive cancer centre. This target number is in line with numbers that have been recruited to the treatment arm in a previous pilot study for people with advanced cancer [15].

Inclusion criteria

- ≥18 years old;
- diagnosis of unresectable, locally advanced NSCLC or metastatic NSCLC;
- ≥6 months post initiation of immunotherapy or targeted therapy or combination chemotherapy/immunotherapy (to avoid sampling individuals immediately after initial diagnosis or immediately upon learning about IT/TT);
- expected prognosis of ≥6 months;
- able to read and write in English;
- able to commit to 3-6 sessions.

Exclusion criteria

- major communication difficulties that would impair ability to engage in a time-limited talking therapy such as significant speech or hearing difficulties;
- cognitive impairment on the basis of a Short Orientation-Memory-Concentration Test (SOMCT) score ≥7 or indicated by the clinical team or medical record

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- currently receiving formal psychological therapy.

Recruitment and consent

Participants will be recruited from outpatient lung cancer clinics, over an anticipated six month period at a comprehensive cancer centre in a large urban setting. Potential participants will be identified by a member of the research team via review of the relevant clinic lists. Eligibility and appropriateness for each potential participant to take part will be confirmed with a lung cancer clinical nurse consultant. The potential participant's treating oncologist may advise the patient of the study, and seek agreement for the research team to contact the potential participant.

Eligible individuals will be called and invited to take part in the study following their lung outpatient appointment unless the treating team advises that the individual does not wish to be contacted. The research team member will describe the study to eligible individuals, conduct the verbal informed consent process, and complete cognitive screening. If the person is eligible and interested in taking part in the study, informed consent will be obtained in accordance with Good Clinical Practice (GCP) guidelines. Signed consent will either be provided in person (if the patient provides consent at time of introduction of the study in person), via mail using a reply-paid envelope to return, or online via email link to a REDCap consent form. Recruitment commenced in July 2022 and is ongoing at the time of submission.

Intervention

CALM is a semi-structured, manualized, individual psychotherapy designed for people with advanced cancer and their loved ones. It shares features with manualized supportive-expressive [16, 17], cognitive-existential [18], and meaning-centred [19] group psychotherapies applied to people with advanced and terminal disease. It was developed based on empirical data, clinical observations, and the theoretical foundations of relational [20], attachment [21] and existential [22] theory. It is informed by the founding team's funded longitudinal research aimed at identifying the antecedents and course of psychosocial morbidity in individuals with metastatic cancer [23-28].

CALM includes 3-6 individual therapy sessions, each approximately 45-60 minutes in length, delivered over 3-6 months. Additional sessions may be offered if clinically indicated. The sessions cover 4 domains: 1) symptom management and communication with healthcare providers; 2) changes in self and relations with close others; 3) sense of meaning and purpose; and 4) the future and mortality [see 11]. All modules will be addressed with each participant, but the sequencing and time devoted to each domain will vary, based on the concerns most relevant to each person. The caregiver of the person with NSCLC (e.g., spouse, adult son/daughter, family member), or other persons accompanying the participant with cancer, are encouraged to participate in one or more of the therapy sessions, as deemed appropriate by the participant with cancer and therapist. CALM can be delivered by specially trained therapists from a wide range of disciplines, including social work, nursing, psychiatry, psychology, and medicine [11]. CALM will be delivered in person, via telehealth (video-call), or by telephone if no alternative is available. The CALM therapists will be provided with a copy of the participant's measures completed at each time point whilst the therapist is still treating the participant, including PHQ-9, DADDS and FACT-G. These are provided to inform clinical treatment and for therapists to discuss with the participant as applicable.

Qualitative interviews

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Qualitative interviews employing cognitive interviewing methodologies will be conducted to assess acceptability of the intervention to people with advanced NSCLC treated with novel therapies.

1. All therapists delivering CALM to study participants will be invited to participate in qualitative interviews through a phone call or email. Therapists involved in this study will be clinical psychologists or clinical nurse consultants who are part of the research team (including authors FL, MD, and MF) and who are: (i) involved in the care of people with advanced or metastatic cancer; (ii) ≥18 years of age; (iii) able to provide informed consent; (iv) fluent in English; (v) willing/able to engage with training in the CALM therapy and attend online supervision meetings (based on feasibility of attending and scheduling in conjunction with concomitant usual role responsibilities). Therapists will complete verbal consent at the start of their interview. Interviews will be conducted following the completion of CALM training. Potential participants will be invited to take part in a semi-structured interview in person, over Microsoft Teams, or over the telephone; verbal consent will be obtained from participating therapists. Consenting therapists' interviews will include questions regarding the therapist's experience with CALM in this cohort, any adaptations they consider needed, and intervention implementation. Therapist-patient relationships and the therapist's perspective of CALM will also be explored. Interviews will be audio-recorded and transcribed for analysis. Demographics will be collected.

2. All participants with cancer will be invited to take part in a semi-structured interview in person, over the telephone, or via telehealth. If participants with cancer agree, their primary carer will also be invited to take part with them. When participants agree, the research team will call the carer to discuss the project in more detail and determine if they wish to participate in the joint interview with the person with cancer. Carers will complete verbal consent at the start of the qualitative interview. Participants with cancer and carers will be asked detailed questions about their experience of the illness and the intervention. They will be asked how they experienced or evaluated: the overall CALM therapy; each of the four CALM dimensions; the therapeutic alliance; and the structure and timeframe of CALM. Interviews will be conducted at completion of the CALM intervention or following study withdrawal.

Interviews will be semi-structured and the interview guide will be revised on a reflexive on-going basis relative to feedback and responses from participants. All interviews will be audio-recorded and transcribed. Recruitment of participants in the qualitative sub-study will continue until thematic saturation is reached.

Evaluation measures and data collection

The measures and data collection, according to the project aims, are described below. Demographic and medical data will be collected, and evaluation measures will be administered to determine the acceptability and potential impact of the intervention. Feasibility of delivering the intervention and of the study protocol will be assessed by evaluation of the uptake, adherence to the intervention, and therapist fidelity in administering the intervention.

Demographics and medical history

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Demographic and clinical characteristics of the participant with cancer will be collected from the participant's medical record and liaison with the treating team after the patient has consented to the project. Data collected will include:

- Age of patient
- Sex
- Treatment received
- Disease status including date of diagnosis with NSCLC, date of diagnosis with advanced or metastatic NSCLC (if not de novo metastatic), date of most recent restaging imaging and outcome (stable disease; partial response; complete response; progressive disease), cranial involvement
- Demographic information such as ethnicity, marital status, education level, and previous psychotherapy received will be obtained through participant verbal self-report during the assessment part of the CALM sessions or at screening.

Measures

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a widely used self-report measure of depression with strong reliability and validity [29]. Scores range from 0-27. Higher scores represent higher levels of depression [29].

Functional Assessment of Cancer Therapy – General (FACT-G)

The FACT-G [30] is a 27-item self-report questionnaire that measures health-related quality of life (HRQOL) across four domains in people with cancer: physical, social, emotional, and functional wellbeing. The FACT-G produces scores on each of the four subscales, as well as a total score. Higher scores indicate higher quality of life. The FACT-G has previously been demonstrated as having high reliability and validity [30].

Death and Dying Distress Scale (DADDS)

The DADDS is a validated 15-item self-report scale measuring death anxiety in people with advanced cancer. The DADDS addresses fears about the dying process and distress about lost opportunities and self-perceived burden placed on others as a result of the possibility of the person with cancer dying from their disease. The DADDS has shown good construct validity with two factors, one related to distress about the shortness of time and the other to distress about dying and death [31, 32].

Clinician Evaluation Questionnaire (CEQ)

The CEQ is a 7-item validated patient-reported experience measure (PREM) [33] that will be completed by participants with cancer to evaluate the extent to which they perceived benefit from the components of the CALM intervention. The CEQ has shown strong internal consistency (Cronbach's alpha = 0.94 to 0.95), factor structure, and concurrent validity [33]. The CEQ will be administered post-intervention.

Patient Experiences Survey

This survey has been purpose built based on previous studies [e.g., 8], in consultation with the lead PI of CALM, Gary Rodin, to determine the experience of participants with cancer of the intervention, including which aspects they found helpful or unhelpful and any changes in their wellbeing following the intervention. This survey consists of nine questions and is expected to take approximately 10 minutes to complete. Participants will be invited to complete the survey within two weeks of

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completing the CALM intervention, or earlier if they withdraw prior to completion of the intervention.

CALM Treatment Integrity Measure (CTIM)

The CTIM [12] is a 32 item questionnaire that assesses treatment integrity of the CALM intervention using eight subscales: 13 items on the therapeutic process subscales: (1) Therapeutic Relationship; (2) Modulating Affect; (3) Shifting Frame; (4) Interpretations; and 19 items on the therapeutic content subscales: (5) Symptom Management and Communication with Healthcare Providers; (6) Changes in Self and Relations with Close Others; (7) Spirituality, Sense of Meaning, and Purpose; (8) Preparing for the Future, Sustaining Hope and Facing Mortality. The CTIM will be completed by the CALM supervisor at each supervision session for each therapist who has presented and will be used to assess fidelity to the intervention and therefore the appropriateness of the CALM intervention for this population. Adherence to the item is estimated on a three-point Likert scale with "1 = needs improvement", "2 = satisfactory", "3 = excellent" implementation of the CALM therapy technique. Items that were not observed in the supervision presentation are left blank indicating that they were not applied. Adherence to the protocol is defined as administering 10/19 items on the therapeutic content subscales in at least 30% of the CTIMs, and 4/19 of these to a satisfactory or excellent extent in at least 30% of the CTIMs, consistent with previous research analysing the treatment integrity according to the first and last CALM sessions [34].

Appropriateness and acceptability

The appropriateness and acceptability of the intervention will be assessed by evaluation of the 1) Patient Experiences Survey, 2) Clinician Evaluation Questionnaire, 3) transcribed qualitative interview data.

Feasibility

Feasibility of the intervention will be assessed by 1) a review of supervisor-rated treatment fidelity using the CALM Treatment Integrity Measure (CTIM) completed after each supervisory session, 2) audio recording all sessions and then reviewing sections of therapy sessions during supervision to check compliance with protocols using the CTIM.

Referral rates/Uptake and Adherence

A Case Report Form (CRF) will be used by the researcher and/or therapist to assess referral rates into the study, uptake of the intervention and participant adherence to the intervention. Reasons for declining to participate will also be noted. The project team, using the CRF will collect variables listed in Supplementary Table 1.

Feasibility outcome criteria are presented in Supplementary Table 2.

Therapist Time

Time and cost of delivering the intervention will be determined based on the number of minutes or hours spent per task costed according to role of the staff member. An outline of the variables to be collected is presented in Supplementary Table 3, and this data will be collected on the Screening Log and CRF.

Impact

The PHQ-9, QUAL-EC, and DADDS will be used for preliminary evaluation of the impact of the intervention and to assess the feasibility of the trial methodology.

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As illustrated in Supplementary Table 4, participants will be asked to complete PHQ-9, QUAL-EC, and DADDS at baseline (T1), immediately post-intervention (T2), 3-months (T3) and 6-months (T4).

Data Analysis

Data will be managed through REDCap [35, 36] and quantitative data analysed using SPSS (version 24) or Excel.

Quantitative analysis

Descriptive statistics

Descriptive statistics (e.g., count/percentage, mean/Standard Deviation, median/interquartile range as appropriate) will be used to summarise demographic, clinical, feasibility data (including time measures), treatment details (modality; if carers were present) and responses to outcome measure questionnaires.

Feasibility

Feasibility data (including time measures) will be analysed using count/percentage. Feasibility outcome criteria are presented in Supplementary Table 2 and these figures are based on previous CALM studies [12, 37-40].

Impact

Change scores will be calculated for participants who complete at least three sessions of CALM as well as for the full sample. Participants who reported a reduction of ≥ 5 points on the PHQ-9 [12] at T2, T3, and T4 compared to baseline will be summarised with a proportion of the sample and 95% confidence interval for the full sample and separately for participants with a baseline PHQ ≥ 8. The proportion and confidence interval will be reported for participants experiencing a 10% or more reduction on the DADDS, or 10% or more increase on the FACT-G. This is consistent with accepted guidelines for interpreting clinically significant changes in patient-reported outcomes [41]. The number and proportion of the sample who have a remission in depressive symptoms of at least threshold severity (indicated by PHQ-9 ≥ 8 points) in those participants with PHQ ≥ 8 at baseline will be reported [as per 12]. Continuous variables will be compared using a paired samples t-test or Wilcoxon signed-rank test as appropriate before and after the intervention, and a Kazis effect size will be reported.

Qualitative analysis

Free text items from the patient experiences surveys and transcribed interviews will be analysed using summarising content analysis. A deductive content analysis approach will be used for coding data. Pre-defined categories will be formulated based on the research questions informing the study. Additional inductive codes will be identified from the survey responses.

Ethics and Dissemination

Data storage and privacy issues.

A unique study identification number system will be used for data collected for this project. This system involves keeping a 'key' that specifies and links the patient's personal identifying information (e.g. names, unique record numbers (URNs)) with the patient's corresponding study identification number (e.g. PT01/ PR01 etc.). The key will be kept electronically (in a password-protected Excel spreadsheet) on a [hospital] server separate from all hardcopy and softcopy data collected.

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Electronic data will be stored in password-protected folders on [hospital]'s secure servers. Identifying information of the patient's name and contact details will be obtained from the medical record and/or consent form only to maintain contact with the patient. This information will not be used in data analysis, and will be deleted from the database at the conclusion of the project.

Only members of the project team and therapists will have access to this data, in accordance with the National Statement on Ethical Conduct in Human Research 2007 and the Australian Code for Responsible Conduct of Research 2018. Hardcopy data will be stored in locked filing cabinets within the [hospital] Department of Psychosocial Oncology. Five years after publication or dissemination of project outcomes, hard-copy and electronic data will be destroyed.

CALM therapists will complete a short documentation on the patient's medical file of each therapy session. This medical file documentation will provide a brief summary of the session as relevant to the treating team. A more detailed therapy note will be completed by the CALM therapist and kept in a password protected file in the research folder accessible only by the research team members. This more detailed note will be sent to AI Professor Gary Rodin before the patient is presented at group supervision to evaluate fidelity of CALM. Research team members will document on the medical file any attempted contact with the patient or research status change (e.g., completed, withdrawn).

Withdrawal criteria.

It is not expected that patients will be withdrawn by the research team or therapist involved in delivering the intervention as the intervention and/or assessment schedule can be modified depending on patient needs. If patients require referral to other practitioners for complementary care (for example, medication), or care for unrelated morbidity, this will be recorded on the database.

Should a participant withdraw from the study, it will be confirmed if they wish to withdraw from: 1) all components of the study; 2) completing questionnaires and interview, but wish to continue therapy sessions; 3) therapy sessions, but willing to complete questionnaires or interviews; or 4) the qualitative sub-study. Patients who opt to withdraw from the study will be asked if they would consent to continue completing follow-up measures, evaluation, and for any of their existing data to be included in analyses. If consent is not given for the latter, their data will be deleted from the database except reasons for withdrawing and demographic details including treatment, sex, age, marital status, highest level of education completed, and previous psychotherapy received. Any electronic or paper records pertaining to their involvement will be destroyed at the completion of the study, except medical notes that have been committed to the electronic system. A record of patients who have withdrawn from the study will be maintained in a secure database until the completion of the study, to ensure that these patients are not approached again by the project team. Patients will be unable to withdraw their data after the completion of the study as their data may have already been used in analyses.

Confidentiality.

It is not expected that participating in this project will pose any risks of harm to participants. If any disclosures of risks to safety (e.g., suicidal ideation) occur during any stages of the project, standard clinical processes will be followed including safety planning with the participant and, when needed, advising an appropriate support person such as a member of the participant's treating team and/or a family member. This limit to confidentiality is included in the Participant Information and Consent Form (PICF).

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Safety reporting.

The potential for adverse events is deemed to be low in this study. Should participants report suicidal ideation while completing the questionnaires (specifically by answering "yes" to question #9 in the PHQ-9), a member of the research or clinical team will follow distress protocols as per usual clinical practice. Specifically, research staff or psychologist will: (i) immediately inform the Principal Investigator and/or most responsible clinician; (ii) contact patient to assess risks and offer a referral to acute services if needed. Any additional action(s) suggested by the Principal Investigator(s) or most responsible clinician will be implemented and documented in the participant's medical file. If a patient scores ≥1 on item 9 of the PHQ-9 completed online via REDCap, an automatic alert will be sent to three members of the clinical research team or clinical psychology CALM project therapists if initial contacts are on leave. The Redcap questionnaires will be turned offline when the project team or clinicians are unable to review the PHQ-9 (e.g., shared leave). Patients will also receive an automated email upon completion of questionnaires thanking them for completing and with crisis numbers should they need them (Appendix Q). Should suicidal ideation be reported directly to CALM therapists by a patient, clinicians will follow regulations from their respective regulating bodies or as otherwise mandated by the law.

Where patients score ≥7 on the SOMCT, the research team will advise their treating team of these results for the treating team to consider and communicate to the patient if appropriate or if further testing is required. Patients will not be advised of their result as the cognitive screening is not a diagnostic tool.

The Sponsor and ethics department will be notified immediately of any safety issues, and the management of these.

Dissemination.

This study will be registered with the Australia New Zealand Clinical Trials Registry. Results from this study will be published in peer-reviewed journals and disseminated at national and/or international conferences. Study findings will also be disseminated to clinicians involved in the care of people with advanced NSCLC.

Discussion

People with advanced NSCLC who are treated with novel therapies face unique psychological concerns that are often unmet in the course of routine care, such as managing uncertainty, dealing with fear of cancer progression, and difficulty obtaining tailored health information [4, 5, 6]. These concerns greatly impact quality of life and therefore establishing evidence for a psychological intervention that is suitable and effective for this cohort is a recommended high priority [6].

CALM has theoretical applicability to this cohort by addressing the dual tasks of focusing on living in the present while preparing for the possibility of disease progression and end-of-life. It is also one of the few interventions developed specifically for people with advanced disease that has been shown to reduce depressive symptoms, 'death anxiety', and improve communication with healthcare providers and preparation for end-of-life [12]. However, CALM has not yet been evaluated specifically in people treated with novel therapies who may face unique challenges of high levels of uncertainty regarding prognosis, potential extended treatment duration and lifespan, and limited healthcare information available. Establishing whether CALM is suitable for people with advanced cancer treated with novel therapies is therefore necessary.

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Our study is an initial step towards understanding if CALM is acceptable to people with advanced NSCLC treated with novel therapies. The results of our evaluation will inform whether CALM requires any adaptations for administration in this cohort. If CALM is shown to be acceptable, and study procedures are feasible, this will inform future studies to assess the efficacy of CALM in people with advanced NSCLC treated with novel therapies.

List of abbreviations

CALM – Managing Cancer and Living Meaningfully

PHQ-9 – Patient Health Questionnaire 9 item

FACT-G – Functional Assessment of Cancer Therapy - General

DADDS –Death and Dying Distress Scale

CTIM – Clinician Treatment Integrity Measure

CEQ – Clinician Evaluation Questionnaire

NSCLC – Non-Small Cell Lung Cancer

CRF – Case Report Form

RCT – Randomised Controlled Trial

IT – Immunotherapy/immunotherapies

TT – Targeted therapy/therapies

PICF – Participant Information and Consent Form

URN – Unique record number

Ethics approval and consent to participate

This study, protocol (V7 as of writing), and all instruments including the informed consent document, have been approved by the Human Research Ethics Committee (HREC) of [hospital] in Melbourne, Australia, HREC reference number: HREC/82047/PMCC. Protocol modifications will be communicated to the reviewing HREC, steering committee, and Principal Investigators.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

The study concept and design were conceived by authors FAL, MJ, GR, MF, MD, JLK, SH, LM, LB, LL, JB, BS, and TS. FAL prepared the first draft of the manuscript. All authors read, edited, and approved the final version.

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Supplementary Table 1. Uptake and adherence data collection

Data	Variables	Collection method	Collection place / time
Referral rates/uptake	No. referred to the intervention	Project specific CRF	Collected during the referral process
	No. who declined referral to the intervention	Screening Log	Collected during the referral processes
	No. who declined the intervention after accepting referral	Project specific CRF	Collected during referral/intervention process
Participant adherence to therapy	No. completing at least 3 sessions of the intervention	Project specific CRF	Collected during individual therapy sessions by clinicians

Note: No. = number; CRF = Case Report Form.

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Supplementary Table 2. Feasibility outcome criteria

Outcome	Value	Feasibility criteria
Recruitment target	20 over 6 months	Recruitment of 20 participants over 6 months
Enrolment rate	20 of 80 (25%)	At least 25% of eligible individuals will be enrolled
Compliance with assessments	12 of 20 (60%)	At least 60% of participants who commence CALM complete the outcome measures at T2
Adherence	13 of 20 (65%) complete ≥3 sessions	At least 65% of participants complete at least three CALM sessions
Therapist time	90 minutes for session 1 (including notes), + 60 minutes per sessions 2-6, + 30 minutes additional time	6 hours for 5 sessions

Note: T2 = post-intervention.

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Supplementary Table 3. Time and costing data collection.

Activity	Variables	Data collected
Intervention delivery	Clinician/researcher time • Session time • Time additional to intervention (e.g., follow up phone calls etc.) • Time for follow-up care discussion at end of intervention, including referrals • Other: free text*	Role (e.g., psychologist, nurse consultant) Time in minutes

*Other: Free text – to collect tasks undertaken that are not otherwise defined.

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Supplementary Table 4. Outcome measures used at each time-point.

Outcome	Baseline (T1)	Post-intervention (T2)	3 months (T3)	6 months (T4)
PHQ-9	x	x	x	x
FACT-G	x	x	x	x
DADDS	x	x	x	x
Patient Experiences Survey		x		
CEQ		x	x	x

Note: PHQ-9 = Patient Health Questionnaire; FACT-G = Functional Assessment of Cancer Therapy; DADDS = Death and Dying Distress Scale; CEQ = Clinician Evaluation Questionnaire.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	13
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	15

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5, 6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	N/A

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	N/A

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		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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BMJ Open

Evaluation of Managing Cancer and Living Meaningfully (CALM) in people with advanced non-small cell lung cancer treated with immunotherapies or targeted therapies: protocol for a single-arm, mixed-methods pilot study

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Manuscripts

Evaluation of Managing Cancer and Living Meaningfully (CALM) in people with advanced non-small cell lung cancer treated with immunotherapies or targeted therapies: protocol for a single-arm, mixed-methods pilot study

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Abstract

Introduction: People with advanced non-small cell lung cancer (NSCLC) treated with immunotherapies (IT) or targeted therapies (TT) may have improved outcomes in a subset of people who respond, raising unique psychological concerns requiring specific attention. These include the need for people with prolonged survival to reframe their life plans and tolerate uncertainty related to treatment duration and prognosis. A brief intervention for people with advanced cancer, Managing Cancer and Living Meaningfully (CALM), could help people treated with IT or TT address these concerns. However, CALM has not been specifically evaluated in this population. This study aims to evaluate the acceptability and feasibility of CALM in people with advanced NSCLC treated with IT or TT and obtain preliminary evidence regarding its effectiveness in this population.

Methods and analysis: Twenty people with advanced NSCLC treated with IT or TT will be recruited from Peter MaCallum Cancer Centre, Melbourne, Australia. Participants will complete 3-6 sessions of CALM delivered over 3-6 months. A prospective, single-arm, mixed-methods pilot study will be conducted. Participants will complete outcome measures at baseline, post-intervention, 3-months, and 6-months, including Patient Health Questionnaire, Death and Dying Distress Scale, Functional Assessment of Cancer Therapy General and Clinician Evaluation Questionnaire. The acceptability of CALM will be assessed using patient experiences surveys and qualitative interviews. Feasibility will be assessed by analysis of recruitment rates, treatment adherence, and intervention delivery time.

Ethics and dissemination: Ethics approval has been granted by the Peter MacCallum Cancer Centre Human Research Ethics Committee (HREC/82047/PMCC). Participants with cancer will complete a signed consent form prior to participation, and carers and therapists will complete verbal consent. Results will be made available to funders, broader clinicians and researchers through conference presentations and publications. If CALM is found to be acceptable in this cohort, this will inform a potential phase 3 trial.

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Strengths and limitations of this study

- The use of mixed methods will capture detailed qualitative and quantitative information on the acceptability of CALM in this cohort.
- The inclusion of outcome measures at multiple time-points allows for full evaluation of the feasibility of this study design to inform a larger trial.
- The primary limitation of this study is the small sample size limiting interpretations on efficacy.
- A second limitation is that people who did not speak, read or write fluently in English were excluded.

Keywords

Non-small cell lung cancer, psychological therapies, CALM, supportive care, immunotherapy, targeted therapy

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Introduction

Advanced non-small cell lung cancer (NSCLC) has historically had a poor prognosis, with five-year overall survival approximately 6% [1]. In recent years, however, improved understanding of molecular subtypes of metastatic NSCLC and the introduction of immunotherapies (IT) and targeted therapies (TT), (subsequently referred to as 'novel therapies'), has improved the prognosis for a subset of people with metastatic NSCLC. For example, five-year overall survival rate is now 62.5% for people with advanced NSCLC with anaplastic lymphoma kinase (*ALK*) translocations who received first-line alectinib [2], and 31.9% for people with cancers that have a programmed death ligand-1 (PDL-1) with tumour proportion score ≥50% who received first-line pembrolizumab [3]. This growing number of people living with advanced NSCLC who experience durable tumour responses to modern treatment approaches may have unique psychological needs [4,5,6,7].

A recent qualitative study of people with NSCLC treated with immunotherapy or targeted therapy found significant unmet needs, including: difficulty managing treatment side effects and toxicities; uncertainty regarding prognosis and treatment duration; not fitting into the 'sick' role; and the emotional strain of seeking tailored health information [4]. Similar concerns have been identified in this cohort in the United States [5, 6], the United Kingdom and Denmark [5]. These concerns can have a significant impact on quality of life, decision-making, and health information-seeking behaviours [5]. There is therefore an urgent need to address the unique psychological concerns of people with advanced NSCLC treated with these novel therapies.

The few psychological interventions trialled in people with metastatic cancer treated with novel therapies have limited their focus to a single area, such as fear of cancer recurrence [8], or promoting hope [9], or have been limited to a single psychological consultation delivered to only two participants [10]. Whilst these have shown promise in addressing these specific areas, they are unlikely to address the broader range of needs identified in the qualitative studies specific to people with advanced NSCLC who have been treated with novel therapies. Managing Cancer and Living Meaningfully (CALM) is a brief evidence-based intervention for people with advanced cancer that has potential to address broader psychological concerns in this population related to four content domains [11]. These are: 1) symptom management and communication with healthcare providers; 2) changes in identity and relationships; 3) sense of meaning and purpose; 4) sustaining hope and facing mortality. CALM is intended to help people attend to the dual tasks of preparing for progressive disease and end-of-life, whilst simultaneously focusing on living (a challenge identified by this cohort [5]). CALM has been shown to reduce depressive symptoms, improve preparation for end-of-life [12] and is associated with subjective improvements in relationships, communication, values identification, and reduced concerns about the future [13].

Though CALM is currently being trialled in other cohorts, such as people with primary malignant brain tumours [14], it has not yet been specifically studied in people with advanced cancer treated with novel therapies. Unlike the cohort in the original CALM randomised controlled trial (RCT) [12] who had a 12-18 month prognosis, people with advanced NSCLC treated with novel therapies may live longer with their disease. It is essential to examine the feasibility and acceptability of CALM in this unique population before undertaking larger-scale studies to evaluate its efficacy.

The overall aim of the present study is to assess the acceptability, feasibility and preliminary evidence of potential impact of CALM in people with advanced NSCLC treated with novel therapies. The specific objectives of this project are to:

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- Assess the feasibility of the CALM intervention, outcome measures, and study design to guide the development of a possible subsequent phase 3 RCT.
- Explore the acceptability of CALM for people with advanced NSCLC treated with novel therapies, their carers, as well as for therapists delivering the CALM intervention.
- Provide preliminary evaluation of the potential impact of CALM in this population.

Methods and analysis

Study design

This study is a prospective, single-arm pilot study. A mixed-methods design will be used. The study protocol adheres to the SPIRIT checklist (see Additional File 1).

Patient and public involvement

This pilot study was conceived and designed by a multidisciplinary group of clinicians, researchers, and people with a lived experience of lung cancer ('patient representatives'). Patient representative co-investigators were intimately involved in the design of this project and will continue to be involved in management oversight through membership of the steering committee. Feedback from participants with cancer and their carers will be provided through a patient experiences survey and qualitative interviews regarding their experience of the intervention and their satisfaction and level of burden with the intervention. This will inform the intervention delivery in a future randomised controlled trial.

Participants

Twenty people with advanced or metastatic NSCLC treated with novel therapies will be recruited from outpatient clinics at an Australian comprehensive cancer centre. This target number is in line with numbers that have been recruited to the treatment arm in a previous pilot study for people with advanced cancer [15].

Inclusion criteria

- ≥18 years old;
- diagnosis of unresectable, locally advanced NSCLC or metastatic NSCLC;
- ≥6 months post initiation of immunotherapy or targeted therapy or combination chemotherapy/immunotherapy (to avoid sampling individuals immediately after initial diagnosis or immediately upon learning about IT/TT);
- expected prognosis of ≥6 months;
- able to read and write in English;
- able to commit to 3-6 sessions.

Exclusion criteria

- major communication difficulties that would impair ability to engage in a time-limited talking therapy such as significant speech or hearing difficulties;
- cognitive impairment on the basis of a Short Orientation-Memory-Concentration Test (SOMCT) score ≥7 or indicated by the clinical team or medical record

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- currently receiving any ongoing formal psychological therapy according to self-report for their cancer or other concerns at the time of consent. If a patient initiated wanting to pause their current therapy to participate in the CALM project for the duration of their CALM participation, this may no longer be an exclusion criteria if deemed clinically appropriate by the research staff member..

Recruitment and consent

Participants will be recruited from outpatient lung cancer clinics, over an anticipated six month period at a comprehensive cancer centre in a large urban setting. Potential participants will be identified by a member of the research team via review of the relevant clinic lists. Eligibility and appropriateness for each potential participant to take part will be confirmed with a lung cancer clinical nurse consultant. The potential participant's treating oncologist may advise the patient of the study, and seek agreement for the research team to contact the potential participant.

Eligible individuals will be called and invited to take part in the study following their lung outpatient appointment unless the treating team advises that the individual does not wish to be contacted. The research team member will describe the study to eligible individuals, conduct the verbal informed consent process, and complete cognitive screening. If the person is eligible and interested in taking part in the study, informed consent will be obtained in accordance with Good Clinical Practice (GCP) guidelines. Signed consent will either be provided in person (if the patient provides consent at time of introduction of the study in person), via mail using a reply-paid envelope to return, or online via email link to a REDCap consent form (see Supplementary Material). Recruitment commenced in July 2022 and is ongoing at the time of submission.

Intervention

CALM is a semi-structured, manualized, individual psychotherapy designed for people with advanced cancer and their loved ones. It shares features with manualized supportive-expressive [16, 17], cognitive-existential [18], and meaning-centred [19] group psychotherapies applied to people with advanced and terminal disease. It was developed based on empirical data, clinical observations, and the theoretical foundations of relational [20], attachment [21] and existential [22] theory. It is informed by the founding team's funded longitudinal research aimed at identifying the antecedents and course of psychosocial morbidity in individuals with metastatic cancer [23-28].

CALM includes 3-6 individual therapy sessions, each approximately 45-60 minutes in length, delivered over 3-6 months. Additional sessions may be offered if clinically indicated. The sessions cover 4 domains: 1) symptom management and communication with healthcare providers; 2) changes in self and relations with close others; 3) sense of meaning and purpose; and 4) the future and mortality [see 11]. All modules will be addressed with each participant, but the sequencing and time devoted to each domain will vary, based on the concerns most relevant to each person. The caregiver of the person with NSCLC (e.g., spouse, adult son/daughter, family member), or other persons accompanying the participant with cancer, are encouraged to participate in one or more of the therapy sessions, as deemed appropriate by the participant with cancer and therapist. CALM can be delivered by specially trained therapists from a wide range of disciplines, including social work, nursing, psychiatry, psychology, and medicine [11]. CALM will be delivered in person, via telehealth (video-call), or by telephone if no alternative is available. The CALM therapists will be provided with

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a copy of the participant's measures completed at each time point whilst the therapist is still treating the participant, including PHQ-9, DADDS and FACT-G. These are provided to inform clinical treatment and for therapists to discuss with the participant as applicable.

Qualitative interviews

Qualitative interviews employing cognitive interviewing methodologies will be conducted to assess acceptability of the intervention to people with advanced NSCLC treated with novel therapies.

1. All therapists delivering CALM to study participants will be invited to participate in qualitative interviews through a phone call or email. Therapists involved in this study will be clinical psychologists or clinical nurse consultants who are part of the research team (including authors FL, MD, and MF) and who are: (i) involved in the care of people with advanced or metastatic cancer; (ii) ≥18 years of age; (iii) able to provide informed consent; (iv) fluent in English; (v) willing/able to engage with training in the CALM therapy and attend online supervision meetings (based on feasibility of attending and scheduling in conjunction with concomitant usual role responsibilities). Therapists will complete verbal consent at the start of their interview. Interviews will be conducted following the completion of CALM training. Potential participants will be invited to take part in a semi-structured interview in person, over Microsoft Teams, or over the telephone; verbal consent will be obtained from participating therapists. Consenting therapists' interviews will include questions regarding the therapist's experience with CALM in this cohort, any adaptations they consider needed, and intervention implementation. Therapist-patient relationships and the therapist's perspective of CALM will also be explored. Interviews will be audio-recorded and transcribed for analysis. Demographics will be collected.

2. All participants with cancer will be invited to take part in a semi-structured interview in person, over the telephone, or via telehealth. If participants with cancer agree, their primary carer will also be invited to take part with them. When participants agree, the research team will call the carer to discuss the project in more detail and determine if they wish to participate in the joint interview with the person with cancer. Carers will complete verbal consent at the start of the qualitative interview. Participants with cancer and carers will be asked detailed questions about their experience of the illness and the intervention. They will be asked how they experienced or evaluated: the overall CALM therapy; each of the four CALM dimensions; the therapeutic alliance; and the structure and timeframe of CALM. Interviews will be conducted at completion of the CALM intervention or following study withdrawal.

Interviews will be semi-structured and the interview guide will be revised on a reflexive on-going basis relative to feedback and responses from participants. All interviews will be audio-recorded and transcribed. Recruitment of participants in the qualitative sub-study will continue until thematic saturation is reached.

Evaluation measures and data collection

The measures and data collection, according to the project aims, are described below. Demographic and medical data will be collected, and evaluation measures will be administered to determine the acceptability and potential impact of the intervention. Feasibility of delivering the intervention and

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of the study protocol will be assessed by evaluation of the uptake, adherence to the intervention, and therapist fidelity in administering the intervention.

Demographics and medical history

Demographic and clinical characteristics of the participant with cancer will be collected from the participant's medical record and liaison with the treating team after the patient has consented to the project. Data collected will include:

- Age of patient
- Sex
- Treatment received
- Disease status including date of diagnosis with NSCLC, date of diagnosis with advanced or metastatic NSCLC (if not de novo metastatic), date of most recent restaging imaging and outcome (stable disease; partial response; complete response; progressive disease), cranial involvement
- Demographic information such as ethnicity, marital status, education level, and previous psychotherapy received will be obtained through participant verbal self-report during the assessment part of the CALM sessions or at screening.

Measures

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a widely used self-report measure of depression with strong reliability and validity [29]. Scores range from 0-27. Higher scores represent higher levels of depression [29].

Functional Assessment of Cancer Therapy – General (FACT-G)

The FACT-G [30] is a 27-item self-report questionnaire that measures health-related quality of life (HRQOL) across four domains in people with cancer: physical, social, emotional, and functional wellbeing. The FACT-G produces scores on each of the four subscales, as well as a total score. Higher scores indicate higher quality of life. The FACT-G has previously been demonstrated as having high reliability and validity [30].

Death and Dying Distress Scale (DADDS)

The DADDS is a validated 15-item self-report scale measuring death anxiety in people with advanced cancer. The DADDS addresses fears about the dying process and distress about lost opportunities and self-perceived burden placed on others as a result of the possibility of the person with cancer dying from their disease. The DADDS has shown good construct validity with two factors, one related to distress about the shortness of time and the other to distress about dying and death [31, 32].

Clinician Evaluation Questionnaire (CEQ)

The CEQ is a 7-item validated patient-reported experience measure (PREM) [33] that will be completed by participants with cancer to evaluate the extent to which they perceived benefit from the components of the CALM intervention. The CEQ has shown strong internal consistency (Cronbach's alpha = 0.94 to 0.95), factor structure, and concurrent validity [33]. The CEQ will be administered post-intervention.

Patient Experiences Survey

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This survey has been purpose built based on previous studies [e.g., 8], in consultation with the lead PI of CALM, Gary Rodin, to determine the experience of participants with cancer of the intervention, including which aspects they found helpful or unhelpful and any changes in their wellbeing following the intervention. This survey consists of nine questions and is expected to take approximately 10 minutes to complete. Participants will be invited to complete the survey within two weeks of completing the CALM intervention, or earlier if they withdraw prior to completion of the intervention.

CALM Treatment Integrity Measure (CTIM)

The CTIM [12] is a 32 item questionnaire that assesses treatment integrity of the CALM intervention using eight subscales: 13 items on the therapeutic process subscales: (1) Therapeutic Relationship; (2) Modulating Affect; (3) Shifting Frame; (4) Interpretations; and 19 items on the therapeutic content subscales: (5) Symptom Management and Communication with Healthcare Providers; (6) Changes in Self and Relations with Close Others; (7) Spirituality, Sense of Meaning, and Purpose; (8) Preparing for the Future, Sustaining Hope and Facing Mortality. The CTIM will be completed by the CALM supervisor at each supervision session for each therapist who has presented and will be used to assess fidelity to the intervention and therefore the appropriateness of the CALM intervention for this population. Adherence to the item is estimated on a three-point Likert scale with "1 = needs improvement", "2 = satisfactory", "3 = excellent" implementation of the CALM therapy technique. Items that were not observed in the supervision presentation are left blank indicating that they were not applied. Adherence to the protocol is defined as administering 10/19 items on the therapeutic content subscales in at least 30% of the CTIMs, and 4/19 of these to a satisfactory or excellent extent in at least 30% of the CTIMs, consistent with previous research analysing the treatment integrity according to the first and last CALM sessions [34].

Appropriateness and acceptability

The appropriateness and acceptability of the intervention will be assessed by evaluation of the 1) Patient Experiences Survey, 2) Clinician Evaluation Questionnaire, 3) transcribed qualitative interview data.

Feasibility

Feasibility of the intervention will be assessed by 1) a review of supervisor-rated treatment fidelity using the CALM Treatment Integrity Measure (CTIM) completed after each supervisory session, 2) audio recording all sessions and then reviewing sections of therapy sessions during supervision to check compliance with protocols using the CTIM.

Referral rates/Uptake and Adherence

A Case Report Form (CRF) will be used by the researcher and/or therapist to assess referral rates into the study, uptake of the intervention and participant adherence to the intervention. Reasons for declining to participate will also be noted. The project team, using the CRF will collect variables listed in Supplementary Table 1.

Feasibility outcome criteria are presented in Supplementary Table 2.

Therapist Time

Time and cost of delivering the intervention will be determined based on the number of minutes or hours spent per task costed according to role of the staff member. An outline of the variables to be

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collected is presented in Supplementary Table 3, and this data will be collected on the Screening Log and CRF.

Impact

The PHQ-9, QUAL-EC, and DADDS will be used for preliminary evaluation of the impact of the intervention and to assess the feasibility of the trial methodology.

As illustrated in Supplementary Table 4, participants will be asked to complete PHQ-9, QUAL-EC, and DADDS at baseline (T1), immediately post-intervention (T2), 3-months (T3) and 6-months (T4).

Data analysis

Data will be managed through REDCap [35, 36] and quantitative data analysed using SPSS (version 24) or Excel.

Quantitative analysis

Descriptive statistics

Descriptive statistics (e.g., count/percentage, mean/Standard Deviation, median/interquartile range as appropriate) will be used to summarise demographic, clinical, feasibility data (including time measures), treatment details (modality; if carers were present) and responses to outcome measure questionnaires.

Feasibility

Feasibility data (including time measures) will be analysed using count/percentage. Feasibility outcome criteria are presented in Supplementary Table 2 and these figures are based on previous CALM studies [12, 37-40].

Impact

Change scores will be calculated for participants who complete at least three sessions of CALM as well as for the full sample. Participants who reported a reduction of ≥ 5 points on the PHQ-9 [12] at T2, T3, and T4 compared to baseline will be summarised with a proportion of the sample and 95% confidence interval for the full sample and separately for participants with a baseline PHQ ≥ 8. The proportion and confidence interval will be reported for participants experiencing a 10% or more reduction on the DADDS, or 10% or more increase on the FACT-G. This is consistent with accepted guidelines for interpreting clinically significant changes in patient-reported outcomes [41]. The number and proportion of the sample who have a remission in depressive symptoms of at least threshold severity (indicated by PHQ-9 ≥ 8 points) in those participants with PHQ ≥ 8 at baseline will be reported [as per 12]. Continuous variables will be compared using a paired samples t-test or Wilcoxon signed-rank test as appropriate before and after the intervention, and a Kazis effect size will be reported.

Qualitative analysis

Free text items from the patient experiences surveys and transcribed interviews will be analysed using summarising content analysis. A deductive content analysis approach will be used for coding data. Pre-defined categories will be formulated based on the research questions informing the study. Additional inductive codes will be identified from the survey responses.

Ethics and dissemination

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Ethics approval and consent to participate

This study, protocol (V7 as of writing), and all instruments including the informed consent document, have been approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee (HREC) in Melbourne, Australia, HREC reference number: HREC/82047/PMCC. Protocol modifications will be communicated to the reviewing HREC, steering committee, and Principal Investigators.

All participants with cancer will complete a signed consent form prior to participation, and carers and therapists will complete verbal consent with a written explanatory statement provided (see Supplementary Material).

Data storage and privacy issues

A unique study identification number system will be used for data collected for this project. This system involves keeping a 'key' that specifies and links the patient's personal identifying information (e.g. names, unique record numbers (URNs)) with the patient's corresponding study identification number (e.g. PT01/ PR01 etc.). The key will be kept electronically (in a password-protected Excel spreadsheet) on a Peter MacCallum Cancer Centre server separate from all hardcopy and softcopy data collected. Electronic data will be stored in password-protected folders on Peter MacCallum Cancer Centre's secure servers. Identifying information of the patient's name and contact details will be obtained from the medical record and/or consent form only to maintain contact with the patient. This information will not be used in data analysis, and will be deleted from the database at the conclusion of the project.

Only members of the project team and therapists will have access to this data, in accordance with the National Statement on Ethical Conduct in Human Research 2007 and the Australian Code for Responsible Conduct of Research 2018. Hardcopy data will be stored in locked filing cabinets within the Peter MacCallum Cancer Centre Department of Psychosocial Oncology. Five years after publication or dissemination of project outcomes, hard-copy and electronic data will be destroyed.

CALM therapists will complete a short documentation on the patient's medical file of each therapy session. This medical file documentation will provide a brief summary of the session as relevant to the treating team. A more detailed therapy note will be completed by the CALM therapist and kept in a password protected file in the research folder accessible only by the research team members. This more detailed note will be sent to AI Professor Gary Rodin before the patient is presented at group supervision to evaluate fidelity of CALM. Research team members will document on the medical file any attempted contact with the patient or research status change (e.g., completed, withdrawn).

Withdrawal criteria

It is not expected that patients will be withdrawn by the research team or therapist involved in delivering the intervention as the intervention and/or assessment schedule can be modified depending on patient needs. If patients require referral to other practitioners for complementary care (for example, medication), or care for unrelated morbidity, this will be recorded on the database.

Should a participant withdraw from the study, it will be confirmed if they wish to withdraw from: 1) all components of the study; 2) completing questionnaires and interview, but wish to continue therapy sessions; 3) therapy sessions, but willing to complete questionnaires or interviews; or 4) the qualitative sub-study. Patients who opt to withdraw from the study will be asked if they would consent to continue completing follow-up measures, evaluation, and for any of their existing data to

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be included in analyses. If consent is not given for the latter, their data will be deleted from the database except reasons for withdrawing and demographic details including treatment, sex, age, marital status, highest level of education completed, and previous psychotherapy received. Any electronic or paper records pertaining to their involvement will be destroyed at the completion of the study, except medical notes that have been committed to the electronic system. A record of patients who have withdrawn from the study will be maintained in a secure database until the completion of the study, to ensure that these patients are not approached again by the project team. Patients will be unable to withdraw their data after the completion of the study as their data may have already been used in analyses.

Confidentiality

It is not expected that participating in this project will pose any risks of harm to participants. If any disclosures of risks to safety (e.g., suicidal ideation) occur during any stages of the project, standard clinical processes will be followed including safety planning with the participant and, when needed, advising an appropriate support person such as a member of the participant's treating team and/or a family member. This limit to confidentiality is included in the Participant Information and Consent Form (PICF).

Safety reporting

The potential for adverse events is deemed to be low in this study. Should participants report suicidal ideation while completing the questionnaires (specifically by answering "yes" to question #9 in the PHQ-9), a member of the research or clinical team will follow distress protocols as per usual clinical practice. Specifically, research staff or psychologist will: (i) immediately inform the Principal Investigator and/or most responsible clinician; (ii) contact patient to assess risks and offer a referral to acute services if needed. Any additional action(s) suggested by the Principal Investigator(s) or most responsible clinician will be implemented and documented in the participant's medical file. If a patient scores ≥1 on item 9 of the PHQ-9 completed online via REDCap, an automatic alert will be sent to three members of the clinical research team or clinical psychology CALM project therapists if initial contacts are on leave. The Redcap questionnaires will be turned offline when the project team or clinicians are unable to review the PHQ-9 (e.g., shared leave). Patients will also receive an automated email upon completion of questionnaires thanking them for completing and with crisis numbers should they need them (Appendix Q). Should suicidal ideation be reported directly to CALM therapists by a patient, clinicians will follow regulations from their respective regulating bodies or as otherwise mandated by the law.

Where patients score ≥7 on the SOMCT, the research team will advise their treating team of these results for the treating team to consider and communicate to the patient if appropriate or if further testing is required. Patients will not be advised of their result as the cognitive screening is not a diagnostic tool.

The Sponsor and ethics department will be notified immediately of any safety issues, and the management of these.

Dissemination

This study will be registered with the Australia New Zealand Clinical Trials Registry. Results from this study will be published in peer-reviewed journals and disseminated at national and/or international conferences. Study findings will also be disseminated to clinicians involved in the care of people with advanced NSCLC.

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Discussion

People with advanced NSCLC who are treated with novel therapies face unique psychological concerns that are often unmet in the course of routine care, such as managing uncertainty, dealing with fear of cancer progression, and difficulty obtaining tailored health information [4, 5, 6]. These concerns greatly impact quality of life and therefore establishing evidence for a psychological intervention that is suitable and effective for this cohort is a recommended high priority [6].

CALM has theoretical applicability to this cohort by addressing the dual tasks of focusing on living in the present while preparing for the possibility of disease progression and end-of-life. It is also one of the few interventions developed specifically for people with advanced disease that has been shown to reduce depressive symptoms, 'death anxiety', and improve communication with healthcare providers and preparation for end-of-life [12]. However, CALM has not yet been evaluated specifically in people treated with novel therapies who may face unique challenges of high levels of uncertainty regarding prognosis, potential extended treatment duration and lifespan, and limited healthcare information available. Establishing whether CALM is suitable for people with advanced cancer treated with novel therapies is therefore necessary.

The use of a mixed-methods design in this study ensures detailed qualitative exploration of the potential acceptability of CALM to people with cancer, their carers, and therapists. The primary limitation of this study is the small sample size of 20 participants, which will limit any interpretations on efficacy of CALM for this population. However, the primary aim of this study is to examine the acceptability and feasibility of CALM and the trial design, and this sample size will allow adequate analyses of these aspects.

The exclusion criteria of this study also limits the generalisability of findings to broader populations. In particular, people who could not speak, read, or write fluently in English were excluded. To date, there were no known studies published on the delivery of CALM with interpreters. Pilot studies to assess the acceptability of CALM with interpreters is a priority area for future work. A further limitation of the study design is the exclusion of people currently receiving formal psychotherapy. This may limit access to cancer-specific psychological support to potential participants who may be already receiving non-cancer related psychological support. This exclusion criterion is needed due to the potential overlap of CALM content domains with other psychological therapies such the focus on relationships, identity, and sense of meaning. However, future work could consider offering participants the opportunity to pause their current therapy if they would like to participate in the CALM study.

Our study is an initial step towards understanding if CALM is acceptable to people with advanced NSCLC treated with novel therapies. The results of our evaluation will inform whether CALM requires any adaptations for administration in this cohort. If CALM is shown to be acceptable, and study procedures are feasible, this will inform future studies to assess the efficacy of CALM in people with advanced NSCLC treated with novel therapies.

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List of abbreviations

CALM – Managing Cancer and Living Meaningfully

PHQ-9 – Patient Health Questionnaire 9 item

FACT-G – Functional Assessment of Cancer Therapy - General

DADDS –Death and Dying Distress Scale

CTIM – Clinician Treatment Integrity Measure

CEQ – Clinician Evaluation Questionnaire

NSCLC – Non-Small Cell Lung Cancer

CRF – Case Report Form

RCT – Randomised Controlled Trial

IT – Immunotherapy/immunotherapies

TT – Targeted therapy/therapies

PICF – Participant Information and Consent Form

URN – Unique record number

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Contributors

FAL contributed to design of proposed study, drafting and revising the paper. MJ contributed to design of proposed study, revising the paper. GR contributed to design of proposed study, design and description of the intervention component, design of qualitative interview scripts, selection of data collection tools, revising the paper. MF contributed to design of proposed study, revising the paper. MD contributed to design of proposed study, planning recruitment procedures, revising the paper. JLK, SH contributed to design of proposed study, population selection and defining inclusion criteria, revising the paper. LM contributed to design of proposed study, revising the paper. LB, LL, JB contributed to design of proposed study, providing a consumer perspective to procedures, revising the paper. TS contributed to writing statistical analysis plan.

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Supplementary Table 1. Uptake and adherence data collection

Data	Variables	Collection method	Collection place / time
Referral rates/uptake	No. referred to the intervention	Project specific CRF	Collected during the referral process
	No. who declined referral to the intervention	Screening Log	Collected during the referral processes
	No. who declined the intervention after accepting referral	Project specific CRF	Collected during referral/intervention process
Participant adherence to therapy	No. completing at least 3 sessions of the intervention	Project specific CRF	Collected during individual therapy sessions by clinicians

Note: No. = number; CRF = Case Report Form.

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Supplementary Table 2. Feasibility outcome criteria

Outcome	Value	Feasibility criteria
Recruitment target	20 over 6 months	Recruitment of 20 participants over 6 months
Enrolment rate	20 of 80 (25%)	At least 25% of eligible individuals will be enrolled
Compliance with assessments	12 of 20 (60%)	At least 60% of participants who commence CALM complete the outcome measures at T2
Adherence	13 of 20 (65%) complete ≥3 sessions	At least 65% of participants complete at least three CALM sessions
Therapist time	90 minutes for session 1 (including notes), + 60 minutes per sessions 2-6, + 30 minutes additional time	6 hours for 5 sessions

Note: T2 = post-intervention.

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Supplementary Table 3. Time and costing data collection.

Activity	Variables	Data collected
Intervention delivery	Clinician/researcher time • Session time • Time additional to intervention (e.g., follow up phone calls etc.) • Time for follow-up care discussion at end of intervention, including referrals • Other: free text*	Role (e.g., psychologist, nurse consultant) Time in minutes

*Other: Free text – to collect tasks undertaken that are not otherwise defined.

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Supplementary Table 4. Outcome measures used at each time-point.

Outcome	Baseline (T1)	Post-intervention (T2)	3 months (T3)	6 months (T4)
PHQ-9	x	x	x	x
FACT-G	x	x	x	x
DADDS	x	x	x	x
Patient Experiences Survey		x		
CEQ		x	x	x

Note: PHQ-9 = Patient Health Questionnaire; FACT-G = Functional Assessment of Cancer Therapy; DADDS = Death and Dying Distress Scale; CEQ = Clinician Evaluation Questionnaire.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

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Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	13
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	15

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		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8

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Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5, 6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	N/A

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		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7

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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	N/A

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		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A

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Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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